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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,855	10/31/2003	Jens Holm	04305/100M237-US1	9333

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EXAMINER	
TSAY, MARSHA M	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,855	HOLM ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-32,52-57,59,73 and 76-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-32,52-57,59,73 and 76-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office Action is in response to Applicants' Amendment received on February 24, 2005. Claims 18, 33-51, 58, 60-72, 74-75 have been canceled. Claims 76-92 are new. Claims 1-17, 19-32, 52-57, 59, 73, 76-92 are pending and under examination.

Priority date is November 1, 2002.

In the previous Office Action, the Examiner mistakenly objected to claims 2-4, 7, 12-13, 16-17, 19, 29 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The instant claims should have been included as rejections under 35 U.S.C. 112, second paragraph, as being dependent on claim 1. The present Office Action currently reflects these changes.

Withdrawal of Objections and Rejections

The objection to the drawings and specification because of minor informalities and various typographical errors is withdrawn.

The objection of claims 3 and 30 because of minor informalities is withdrawn.

The rejection of claims 5-6, 8, 11-12, 26-27 under 35 U.S.C. 112, second paragraph, as being indefinite in the Office Action dated November 22, 2004 is withdrawn. The instant claims are, however, rejected in the present Office Action as being dependent on claim 1. Please see the 35 U.S.C. 112, second paragraph rejections, below.

Maintenance of Objections and Rejections/New Objections and Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 19-32, 52-57, 59, 73, 76-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a recombinant protein variant with the ability to induce a protective immune response to a naturally occurring allergen. The use of the term "protective" renders the claim unclear. It is hard to establish whether an immune response is protective or not because several factors need to be assessed, such as concentration of antigen, binding of antigen to specific antibodies, the number and type of antibodies stimulated, and the activation of B and T cells. The recombinant protein variant may induce an immune response, but to deem the reaction as protective renders the claim indefinite. In the first Office Action dated November 22, 2004, Examiner acknowledged that on page 43 of the specification, Applicants do provide a definition of "protective" immune response. However, the definition is broad in view. For example, Applicants disclose the "protective immune response is thought to be mediated largely by generation of a large number of IgG antibodies that presumably block the interaction between allergen and IgE antibodies". Applicants do not define a specific number of IgE antibodies that are generated and at which level the generated IgE antibodies constitute a "protective" response. Applicants also disclose a "protective immune

response most likely involves stimulation of T-cells". Applicants do not address the number of stimulated T-cells that necessary to raise a "protective" immune response.

Also, as previously stated in the Office Action dated November 22, 2004, Claim 1 is drawn to a primary mutation of a scaffold protein wherein the mutated amino acid is identical or homologous to the corresponding residue on the naturally occurring allergen. It is unclear what the purpose of introducing an identical amino acid to a scaffold protein can serve. If the amino acid introduced is identical, then the scaffold protein will not be a variant and will have the same properties as the naturally occurring allergen. In addition, it is unclear what a "homologous" amino acid is. Amino acids are traditionally grouped together based on hydrophobicity, hydrophilicity, acidity, and basicity and are not characterized by being homologous.

Claims 2-17, 20-24, 27, 29, 55-57, 59, 73, 76-92 are included in this rejection because they are dependent on claim 1.

Claim 19 is also drawn to a protective immune response. Please see the claim 1, 112-2nd rejection, for the use of the term "protective".

Claims 25, 28, 30-32 are drawn to the mutations of a protein variant. The claims list primary and secondary mutations but do not identify a SEQ ID number or reference from which the mutations can read on. It is unclear what the mutations are drawn to because as disclosed, the mutations are drawn to a residue on an unidentified amino acid sequence. Applicants assert claims 25 and 28 depend from claim 24, and accordingly, are directed to mutations in Mal d 1. Similarly, claims 30-32 depend from claim 29, and are directed to mutations in Dau c 1. Applicants further assert Mal d 1

and Dau c 1 are well known in the art and draw attention to the Accession numbers provided in the specification. Examiner acknowledges the disclosure of the Mal d 1 and Dau c 1 Accession numbers in the specification, p. 29-30. However, as disclosed in the specification, there is more than one accession number for the various isoforms of Mal d 1 and Dau c 1. Since the isoforms of Mal d 1 and Dau c 1 have different Accession numbers, they must also have different amino acid sequences. Claims 24 and 29 only identify the scaffold protein is Mal d 1 and Dau c 1, without reference to an Accession number. Therefore, it is unclear if the primary mutations as listed in claims 25, 28, and 30-32 are applicable to each of the Mal d 1 and Dau c 1 isoforms and/or Accession numbers since specific amino acid residues are recited. Therefore, the claims should be corrected to include the relevant amino acid sequence to which the protein variant is drawn to because the polypeptide sequence is essential to the function of the invention.

Claim 26 is drawn to at least two primary mutations selected from the group consisting of (E76H, E76R, E76K, Q76H). It is unclear which residue Q76H is referring to since residue 76 has already been recited as glutamic acid (E).

Claims 52-54 are drawn to a primary mutation of a scaffold protein wherein the mutated amino acid is identical or homologous to the corresponding residue on the naturally occurring allergen. Please see the claim 1, 112-2nd rejection, for the same issues regarding identical or homologous amino acids.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-6, 9-10, 20-22, 55-56, 59 are again rejected under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (US 5583046). Valenta et al. teach recombinant protein variants that exhibit the same or similar antigenic properties as birch pollen P14, as well as to other allergens in the Fagales order, wherein the polypeptide comprises at least one epitope of these allergens (col. 2, lines 14-25, lines 63-67; claims 1, 9-10, 20-22). Valenta teach a computer search for proteins whose sequences share homology with birch P14 and a significant homology between P14 and a cytoskeletal protein, profilin, is present (col. 3, lines 56-63, col. 5, fig. 5, col. 6, fig. 12; claims 1, 20-22). Valenta et al. teach the expression of a protein having at least one epitope of the P14 allergen where the 3^{l}-region of PC14 cDNA (bp 419-478) was cloned in the EcoRI site of lambda gt11 and expressed as an IgE-binding polypeptide (col. 8, lines 54-67; claims 1, 20-22). In Fig. 12 (col. 10, lines 31-47; claim 1), Valenta et al. teach IgE-binding capacity with nonrecombinant and recombinant P14 and human prolifin, where cross-reactivity was shown for strips 1 (P14 and Bet v 1) and 2 (P14) (col. 6, lines 40-44). Valenta et al. teach methods of administration using P14 synthetic polypeptide allergens to hyposensitize or desensitize a mammal, either alone or with a pharmaceutically acceptable carrier (col. 11, lines 35-40; claims 55-56, 59).

On page 21, section B, of the Remarks dated February 25, 2005, Applicants assert Valenta et al. do not teach the use of a scaffold protein to maintain the three-

dimensional folding pattern of the allergen. Although Valenta et al. do not specifically teach the structural similarity between the recombinant protein variants versus native birch pollen P14, the tertiary structure of the protein variants is inherently similar to the native birch pollen as concluded from the results of the IgE immunoblots. For example, in Fig. 1B (col. 4, lines 65-70), Valenta et al. teach binding of patients' IgE to mugwort profilin can be blocked with recombinant birch profilin and purified grass profilin, therefore demonstrating common IgE binding properties of these related proteins and thus, showing that they are structurally similar.

Applicants assert Valenta et al. teach only proteins with amino acid homology. In col. 9, section 5.7, Valenta et al. teach polypeptides homologous to P14 within the order Fagales and in section 5.9, Valenta et al. teach the expression of P14 coding cDNA in *E. coli* as fusion or nonfusion protein and detection of IgE-binding capacity of these polypeptides. Each of these polypeptides can be or are variants of proteins of alder, hazel, and hornbeam, which are homologous to P14 allergen, hence they are variants of a scaffold protein as defined by Claim 1.

Applicants also assert Valenta et al. do not teach the insertion of mutations in the scaffold protein. Claim 1 currently recites a recombinant protein variant which comprises two or more primary mutations spaced by at least one non-mutated amino acid residue, the primary mutations are at least one amino acid residue identical or homologous to the amino acid residue or residues in corresponding position in the naturally occurring allergen. Thus, the primary mutation can actually be an amino acid that does not change and is identical to the amino acid on the native allergen. The

synthetic polypeptides created in the Valenta et al. invention comprise proteins having at least one epitope of the P14 molecule. Therefore, the amino acid sequence of the recombinant protein variant created by Valenta et al. comprise the two or more primary mutations as defined in Claim 1. Applicants also assert the polypeptides of Valenta et al. have the same or similar antigenicity as the native allergen, while the instant claims are drawn to an increased or decreased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring antigen. Valenta et al. teach the results of IgE immunoblots, cross-inhibition tests, clinical tests and Northern (RNA) blots indicate this invention provides polypeptides which exhibit the same or similar antigenicity as the related P14 pollen allergens of birch, alder, hazel, etc. Valenta et al. teach the terms "same" and "similar." The use of the term "similar" suggests that the polypeptides are not completely identical in antigenicity, therefore being similar can comprise an increase in affinity or binding capacity (Fig. 1B, 13).

Claims 1, 5-6, 8-9, 15, 20-24, 52 are rejected again under 35 U.S.C. 102(b) as being anticipated by Son et al. (Son et al., 1999, Eur. J. Nutr. 38 : 201-215). Son et al. teach recombinant protein variants from 12 Mal d 1 clones derived from seven different apple strains and from Bet v 1 clones (p. 203; claims 1, 9, 20-24). Mal d 1 and Bet v 1 share a degree of 55-68% amino acid sequence identity (p. 202 intro.). Son et al. teach the amino acid sequences of the different Mal d 1 clones and the minor deviations between the clones (p. 206 results, p. 207 fig. 2), as well as the differences in amino acid identity between the Bet v 1 clones (p. 208 fig. 3, p. 209 table 1). To study IgE

binding and cross-reactivity, Son et al. teach mutated allergens of Mal d 1 and Bet v 1 by site-directed mutagenesis (p. 208; claims 1, 5-6, 15, 20-24, 52). Son et al. teach IgE binding capacity of the recombinant allergens and mutants of Mal d 1 and Bet v 1 by enzyme allergosorbent test wherein the recombinant allergens with high IgE binding are categorized in class 3-4 and those with decreased IgE binding are categorized in class 0-2 (p. 211 table 2; p. 212 table 3). Note in particular, the high IgE binding capacity of the Mal d 1 isoallergen clones GD26 and GS29 (p. 211, table 2; claim 1, 8).

Applicants assert Son et al. teach, at best, the use of native allergens in which point mutations are inserted. According to Applicants, the present invention teaches the use of a scaffold protein that maintains the three-dimensional folding pattern of the allergen, and the introduction of point mutations into the scaffold protein, not the allergen itself. On page 11, line 15, of the specification, Applicants disclose "the idea behind the present invention is to select a naturally occurring 'scaffold protein' with sequence homologies to the natural allergen." Furthermore, on page 29, line 25, Applicants disclose in "other preferred embodiments, scaffold proteins of the major birch pollen allergen Bet v 1 are e.g. ...isoforms of Mal d 1 (apple) exemplified by accession numbers...isoforms of Dau c 1 (carrot) exemplified by accession numbers...." Son et al. teach different Mal d 1 and Bet v 1 isoforms and mutants were cloned and produced as bacterial recombinant proteins (p. 203). Son et al. teach point mutations were introduced into Mal d 1 and Bet v 1 clones (p. 202). Therefore, the recombinant protein variants of Son et al. do meet the present invention's definition of a scaffold protein

because they are isoforms of a natural allergen, wherein point mutations have been introduced.

Applicants also assert Son et al. do not teach that mutations inserted into a scaffold protein would increase or decrease the binding affinity of IgE specific to the native allergen. However, as explained in the 35 U.S.C. 102(b) rejection above, Son et al. do teach IgE binding capacity of recombinant allergens and mutants. On pages 210-211, Son et al. teach IgE binding capacity of recombinant allergens and mutants are investigated by immunoblotting and by enzyme allergosorbent test. Son et al. teach their mutation studies show that positions 112 in Bet v 1 and 111 in Mal d 1 are "hot spots" for IgE reactivity (p. 214). For example, in the case of Bet v 1, clone B2 was used as template and stepwise mutated to the Bet v 1a sequence, the drastic differences between the IgE binding to mutated allergens B2P and B2S which differed in one amino acid demonstrated that proline in position 112 is a key residue for 'hypoallergenicity' (p. 214).

Finally, Applicants assert that the point mutation inserted into a naturally occurring allergen as performed by Son et al. is not a desirable approach, as disclosed in the instant specification (p. 11, lines 7-13). Applicants disclose that "a major disadvantage of this approach is that by introducing an increasing number of mutations into the allergen, the risk of destabilizing the three-dimensional structure of the molecule is greatly increased...." Son et al. do not introduce an increasing number of point mutations into the Mal d 1 or Bet v 1 isoforms. Son et al. teach a single point mutation

in various Mal d 1 and Bet v 1 isoforms, therefore greatly decreasing the risk of destabilizing the three-dimensional structure of the scaffold protein, if any.

Claims 54, 73 are rejected again under 35 U.S.C. 102(b) as being anticipated by King et al (King et al. 2001 J. Immun. 166(10): 6057-6065). King et al. teach modified recombinant allergens with reduced allergenicity while retaining immunogenicity of the natural allergens. King et al. teach hybrid proteins consisting of a portion of a guest allergen of interest and a portion of a homologous protein. King et al. describe the function of the homologous protein as a scaffold to maintain the native structure of the guest allergen of interest (p. 6057). King et al. identify the guest allergen Ag 5 from yellow jacket is Ves v 5 and the homologous host allergen to be Pol a 5, a paper wasp venom protein (p. 6057). King et al. teach Ves v 5 and Pol a 5 have a sequence identity of 59% and several hybrids of the two proteins (p. 6058, fig. 1; claim 54). King et al. teach the recombinant Ag 5s and hybrids show nearly identical CD spectra as those of the natural Ag 5s (p. 6060, figure 4; claim 54). The results in Table IV show that the hybrids EA-PV_{1-46}, EA-PV_{1-155}, and EA-$PV_{156-204}$ induced hybrid-specific, as well as vespid Ag 5-specific, T cell responses (p. 6063, Table IV; claim 73).

On page 22, section D, of the Remarks dated February 25, 2005, Applicants assert claim 54 has been amended to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue." However, the amended changes are currently not present on claim 54. Claim 54 is currently amended to

remove indefiniteness due to the use of the term "preferable." Applicants also assert that King et al. is directed to hybrid constructs wherein a scaffold protein is substituted with relatively long stretches of amino acids of a native allergen, and therefore does not contain "two or more primary mutations spaced by at least one non-mutated amino acid residue." King et al. would still meet this limitation, however, because as recited in claim 54, the primary mutation is an amino acid residue that is identical or homologous to at least one amino acid residue present in the corresponding position in the natural occurring allergen. Therefore, the primary mutation can actually be an amino acid that does not change and is identical to the amino acid on the native allergen.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 16, 2005

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER